F.A.O. Ruth O'Reilly
FAX [redacted]

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Queen's University Belfast

united hospitals

Dr J G Jenkins MD FRCP FRCPCH FRCPI
Paediatric Department, Antrim Hospital, ANTRIM BT41 2RL
E-mail address: [redacted] Tel: [redacted]

Dr E Sumner MA BM BCh FRCA
[redacted]

28th June 2004

Dear Dr Sumner (for information)

Thank you for your letter dated 11th June 2004, in which you express your great unease regarding the understanding of the basics of fluid management and their implementation in clinical practice in children and young people. As you copied your letter to Dr Campbell, CMO I felt it best to discuss the points you have raised with her before replying.

Indeed, in the interim, the results of a N. Ireland regional audit have also become available, assessing the implementation of the hyponatraemia guidelines issued by DHSSPS in early 2002. These show an encouraging level of compliance with the guidelines in paediatric units across the province, but do also identify some situations in which the guidelines do not appear to have been fully followed. It appears that this is not a problem unique to Northern Ireland, as shown by the attached letter published in Archives of Disease in Childhood in July 2003, relating to the death of a child from hyponatraemia in a major paediatric teaching hospital in England. We have also become aware of issues relating to the use of oral fluids and the potential for complications to arise when these are administered (often by parents) to children receiving IV fluids. These are often hypotonic as many children refuse to drink proprietary oral rehydration formulas, and we believe that this issue will also be worthy of further attention. In addition, concerns have recently been expressed by colleagues in adult specialties regarding care of children requiring intravenous fluids who come under their care, often in an adult environment.

In recognition of the concerns which have become apparent from all of these sources we feel that there are a number of actions which need to be taken. I understand that Dr Campbell will be making arrangements for a workshop at which issues of fluid management can be discussed between colleagues in relevant specialties within medicine, and indeed nursing. In addition, I have already highlighted with the General Medical Council the importance of specific reference to education and training in fluid administration and management for doctors in the PRHO grade, as part of the current

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revision of 'The New Doctor'. It will be helpful if the importance of this is also raised with the GMC by others, possibly including Mr Leckey and yourself. We will also bring this issue to the attention of the Northern Ireland Postgraduate Dean and Director of Undergraduate Medical Education, so that it can be raised with relevant individuals and committees who have responsibility for both undergraduate and postgraduate training.

When the audit results were presented in my own unit last week we agreed with our nursing colleagues that a formal morning and evening handover of fluid management involving relevant medical and nursing staff should be introduced for all children receiving intravenous fluids.

We are very grateful for the time you have given to helping identify these important issues, and guiding our thinking towards developing solutions. I hope that the steps set out above will show that this is a subject which the profession in Northern Ireland are taking very seriously, not just with the rapid development and circulation of the 2002 guidelines and the subsequent editorial in the November 2003 Ulster Medical Journal, but also with the regional audit which has subsequently been undertaken, and our plans to follow this up in the ways I have outlined. We will of course be delighted to hear of any other ways in which you feel we could usefully take this issue forward.

With best wishes,

Yours sincerely

Dr John Jenkins.
Senior Lecturer in Child Health & Consultant Paediatrician

cc Dr H Campbell CMO
Mr J Leckey HM Coroner

July 2003.

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Table 1 Children with CF and renal failure associated with antibiotic treatment

Patient	Age	Weight (kg)	Other related problems	Pre-antibiotic plasma Cr (μmol/l)	Antibiotics used (mg/kg/day)	Dose adjusted to raised Cr	Biopsy findings	Peak Cr (μmol/l)
1	6 y	23	Liver disease; Constipation	64	Gentamicin 10; Cefuroxime 200	Stopped	ATN	862 (D16)
2	4 mth	5.6	Diarrhoea	49	Gentamicin 8.5; Ceftazidime 130	Course already completed	Not done	494 (D19)
3	7 y	22	Pseudo Bartter syndrome	NR	Gentamicin 12; Ceftazidime 150		ATN	776 (D22)

Patient	Outcome at 3 months; Cr (μmol/l)	Treatment	Cr (μmol/l)	Gentamicin levels (mg/l)
1	43	Conservative	139 peak	13.9 peak (D8)
2	55	PD for 5 days	162 random	16.2 random (D18)
3	50	HD for 4 days	10 peak; 2.1 trough	10 peak; 2.1 trough (D2)

*Only out of range/inappropriate gentamicin levels tabulated. Cr, creatinine; ATN, acute tubular necrosis; NR, not recorded; PD, peritoneal dialysis; HD, haemodialysis; D, day.

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Authors' reply

Dr Biban states that we did not adequately emphasise the neurologic side effects of interferon treatment. Although it has been reported that interferon alpha has been responsible for various neurologic side effects, there are no clear data indicating the frequency of these in children. Short term interferon therapy has been safely used at our department in treating various different conditions, particularly in the complex hemangiomas for many years. No side effects of interferon therapy except mild fever, malaise, leukopenia, and elevation of liver transaminases have been observed. These were reversible by stopping therapy for a short period. In one patient who received long term interferon therapy, peripheral neuropathy developed during the treatment.

This patient was a 15 year old boy with Hodgkin's disease who received interferon as an adjuvant immunotherapy post autologous stem cell transplant. Peripheral neuropathy developed 20 months after IFN treatment.[1] A large cumulative dose combined with the prolonged treatment may have had an important role in this complication in our case. We concluded that the use of interferon in children affected by KSM or in children with various benign tumours containing vascular elements is still a good therapeutic alternative. If the duration of treatment and the cumulative doses of interferon are closely monitorised, severe neurologic side effects during IFN therapy would not be an important problem. As the use of interferons in various conditions gradually expands, the data related to the adverse neurologic side effects will increase and be better understood.

S Emir, C Akyüz
Department of Paediatrics, Ankara University, Ankara, Turkey

Correspondence to Dr Emir, Ankara University Faculty of Medicine, Department of Paediatrics, Cebeci, Ankara, Turkey; emirs@ttnet.net.tr

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Acute renal failure and cystic fibrosis

It is surprising that there are few reports of acute renal failure (ARF) in children with cystic fibrosis (CF) given the large number of antibiotic courses prescribed and the possibility of either direct toxicity from aminoglycosides or the occurrence of interstitial nephritis. The registry of our regional paediatric renal unit shows no cases of ARF in a CF patient between 1985 and 1998, but three cases between 1999 and 2001, all of whom had received gentamicin and ceftazidine.[1]

Over the past nine months we have been referred three additional CF patients who had been treated with a combination of gentamicin and ceftazidine/cefuroxime (table 1). The initial doses of antibiotics used to treat the patient were within UK guidelines,[2] but the gentamicin levels were raised. All six children had received a number of other medications including, in some instances, other antibiotics prior to the gentamicin and cephalosporin combination. Only one of the four biopsy specimens revealed interstitial nephritis in addition to the acute tubular necrosis (ATN) changes found in all four. All six children have made a good renal recovery with normal blood pressures and creatinine levels at three months.

A recent e-mail survey of members of the British Association for Paediatric Nephrology revealed four other cases of ARF with combination antibiotic therapy in CF patients (three of four with ceftazidine and gentamicin). The increased incidence points to the need for increased vigilance when gentamicin and cephalosporin combinations are used to treat exacerbations, particularly if there is a potentially dehydrating state or pre-existing renal anomaly. The cases have been reported to the Committee for the Safety of Medicines and we suggest a national monitoring programme should be instigated.

J Drew, A R Watson, A Smyth
Children & Young People's Kidney Unit, Hucknall Road, Nottingham NG5 1PB, UK

Correspondence to: Dr A R Watson; jhayes1@nchf.trent.nhs.uk

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Fatal iatrogenic hyponatraemia

We recently cared for a 13 month old girl admitted to hospital following a short history of diarrhoea and vomiting. Clinical examination revealed lethargy and moderate dehydration. Initial serum sodium was 137 mmol/l and she was commenced on intravenous fluids using 4% dextrose/0.18% saline.

Twelve hours after admission the child suffered a generalised tonic-clonic seizure at which time the serum sodium was found to be 120 mmol/l. Unfortunately, the child went on to have a respiratory arrest, developed fixed dilated pupils, and died despite full intensive care. An extensive postmortem examination revealed only diffuse cerebral swelling with necrosis of the cerebellar tonsils.

It is well recognised that symptomatic hyponatraemia can result in significant morbidity and mortality in previously healthy children[1–3] and adults.[4] The administration of hypotonic intravenous fluids to children can be fatal and the reasons for this have been well documented for several years. Many physiological stimuli encountered during acute illness result in the non-osmotic release of antidiuretic hormone; these include pyrexia, nausea, pain, reduced circulating volume, and the postoperative state. The administration of hypotonic intravenous fluids in

these circumstances results in the excretion of hypertonic urine, the retention of free water, and the development of hyponatraemia.[4]

Despite clear and repeated warnings over the past few years,[1–7] the routine administration of 4% dextrose/0.18% saline remains standard practice in many paediatric units. This practice is based on formulas developed for calculating maintenance fluid and electrolytes in healthy children over 40 years ago and there seems little understanding of the potential risks associated with their use during acute illness.

A global change of clinical practice is required to prevent these needless deaths. This is a challenge that the RCPCH should face up to, together with the Medicines Control Agency and the National Patient Safety Agency. A useful first step would be to label bags of 4% dextrose/0.18% saline with the warning that severe hyponatraemia may be associated with its use.

S Playfor

Consultant Paediatric Intensivist, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA, UK; Stephen.Playfor@CMMC.nhs.uk

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Thyroid screening in Down's syndrome: current patterns in the UK

Children and adults with Down's syndrome are at increased risk of developing thyroid dysfunction, and screening for thyroid dysfunction is recommended as part of their health surveillance.[1] Clinical history and examination are known to be unreliable indicators of thyroid dysfunction in Down's syndrome. Venous blood for thyroid stimulating hormone (TSH) assay remains the gold standard. Capillary blood spot on filter paper TSH has been proposed as a simpler and more convenient alternative screening method for hypothyroidism in these children.[2]

To establish current screening practices, we undertook a postal questionnaire of community paediatricians registered with the British Association for Community Child Health (BACCH). Community paediatricians are the group most likely to see children with Down's syndrome for health surveillance. Paediatricians were asked whether they routinely screened children with Down's syndrome for thyroid dysfunction. They were asked at what age of child they began screening, how often they screened, and which method they used.

The questionnaire response rate was 64% (209/325). All the paediatricians who returned completed questionnaires routinely looked after children with Down's syndrome. As expected, almost all of respondents, 93% (194/209), were screening routinely. Most paediatricians began screening before 5 years of age, and screened every two years (table 1). Venous blood TSH was the most frequently used method of screening (83%, 174/209). Only a small number have begun using capillary blood spot on filter paper TSH (7%, 15/209). A few paediatricians were relying on clinical suspicion alone. Those paediatricians not routinely screening for thyroid dysfunction, were either measuring TSH opportunistically or were undertaking biochemical screening only when symptoms or signs raised suspicion.

The Down's Syndrome Medical Interest Group (DSMIG) has recommended biochemical screening for thyroid dysfunction at least every two years after the first year of life.[1] Most paediatricians' practice is consistent with this recommendation. Capillary blood sampling has practical advantages over venous sampling, with regard to patient acceptability, particularly in adolescents with Down's syndrome and with regard to cost. There is growing evidence that capillary blood spot TSH is a reliable screening tool for thyroid dysfunction in children with Down's syndrome.[3–4] Capillary blood spot TSH may, in the future, come to replace venous TSH sampling in children with Down's syndrome.

S Varadkar, G Bingham, D Lessing
Hounslow & Spelthorne Community & Mental Health NHS Trust and West Middlesex University Hospital, Isleworth, UK

Correspondence to: Dr S Varadkar, Biochemistry, Endocrinology and Metabolism Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; sophia@varadkar.co.uk

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Changes in serum sodium levels during treatment of hyperglycaemia

Carlotti *et al*[1] state that fluid and electrolyte management might contribute to the development of cerebral oedema in hyperglycaemia. There is a simple rule of thumb, formulated by Katz, which may help calculate water and electrolyte deficits and predict the changes in sodium levels which accompany changes in glucose levels,[2] namely that a decrease of 0.29 mmol/l in serum sodium may be expected for every 1.0 mmol/l increment in serum glucose.

This may be explained as follows: hyperglycaemia causes an osmotic movement of water out of the cells, which leads to hyponatraemia by dilution. Thus, at presentation, the patient is usually severely dehydrated intracellularly. However, the serum sodium is lower than would be expected because of this dilution of the extracellular fluid. When the patient is treated with insulin, glucose enters the cells, taking water with it, leading to a relative concentration of the extracellular fluid, and thereby a rise in serum sodium. This rise may be predicted and calculated using Katz's formula.[2]

Carlotti *et al* also comment on the report of Glaser *et al* that the chance of cerebral oedema during treatment is increased in children who present with high initial serum urea levels and when there is a lack of an increase in serum sodium levels during treatment.[3] This increased risk may be explained by the fact that the urea level rises in proportion to the degree of dehydration. Urea contributes to serum osmolality and if the fall in urea is not taken into account the serum osmolality may be allowed to drop too rapidly, thereby increasing the risk of cerebral oedema. Carlotti *et al* do not take this into account in their formula for calculation of osmolality. The calculation of serum osmolality as twice the sum of sodium and potassium plus the urea and glucose levels (all in mmol/l) corresponds better with the formally measured osmolality.[4]

By treating hyperglycaemia using hypotonic solutions or glucose alone, the serum osmolality will fall rapidly and thereby increase the risk of cerebral oedema.

Serum osmolality must be monitored frequently, either by direct measurement or calculation from the sodium, potassium,

Table 1 Results of completed questionnaires (n=209)

Age screening initiated (y)	No. (%)	Screening frequency	No. (%)	Screening method	No. (%)
<5	167 (80%)	Yearly	35 (17%)	Venous TSH	174 (83%)
5–10	28 (13.5%)	Two yearly	115 (55%)	Capillary blood spot TSH	15 (7%)
>10	1 (0.5%)	Three yearly	20 (10%)	Both venous and capillary blood spot TSH	4 (2%)
No data	13 (6%)	Opportunistically	17 (8%)	Clinical history and examination only	3 (1.5%)
		Other	10 (4.5%)	No data	13 (6.5%)
		No data	12 (5.5%)		

TSH, thyroid stimulating hormone.